General

Guideline Title

Venous thromboembolism and hormone replacement therapy.

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Venous thromboembolism and hormone replacement therapy. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 May. 16 p. (Green-top guideline; no. 19). [87 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Royal College of Obstetricians and Gynaecologists (RCOG). Hormone replacement therapy and venous thromboembolism. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2004 Jan. 9 p. (Guideline; no. 19).

Recommendations

Major Recommendations

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Classification of evidence levels (1++ to 4) and grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

How Should Venous Thromboembolism (VTE) Risk Be Approached When Hormone Replacement Therapy (HRT) Is Being Considered?

A - Women starting or continuing HRT should be counselled with regard to the perceived benefits and possible risks for their individual situations, including consideration of alternative therapies.

Do HRT Type and Duration Influence VTE Risk?

The Influence of Estrogen Type

D - The risk of VTE may be less with esterified estrogens compared with conjugated equine estrogen.

The Effect of Combination HRT

C - There may be a greater risk of VTE with combination therapy and definitive information on individual estrogen types is still lacking. However, the results to date suggest that therapy with estrogen alone is associated with a significant VTE risk.

VTE Relationship to Estrogen Dose

D - There is some evidence that the effect of estrogen therapy may be dose related.

Duration of Therapy

B - The risk of VTE is highest in the 1st year of HRT use, with no evidence of continuing risk on stopping HRT.

What Is the Role of Screening for Heritable Thrombophilia When Assessing the VTE Risk Associated with HRT?

C - Universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of HRT is inappropriate.

There is limited information on the natural history of thrombophilias, the mechanism of estrogen-associated thrombosis and how these two factors interact. The absolute risk of VTE with HRT is, however, low. The cost-effectiveness of screening women for thrombophilia has been examined in a number of at-risk clinical circumstances and screening selected women before prescribing oral HRT may be the most cost-effective method. However, on the available evidence, universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of HRT is inappropriate and should be discouraged.

D - In women without a personal history of VTE but with a high-risk thrombophilic trait (such as deficiency of antithrombin, protein C or protein S) that has been identified through screening because of a symptomatic family member, oral HRT should be avoided and specialist advice sought.

Where there is no personal history of VTE but an underlying thrombophilic trait is identified through screening carried out because a first-degree relative has a history of previous VTE (e.g., apparently spontaneous VTE, or VTE at a young age, or VTE events in two or more family members), HRT should be avoided in high-risk situations such as type 1 antithrombin deficiency or combinations of defects. Specialist advice should be sought. With other thrombophilic defects, there is insufficient evidence at present to indicate that HRT should be completely avoided, although, as noted above, evidence indicates around an overall eight-fold increase in risk of VTE. An assessment of other risk factors for VTE should be made. In the presence of multiple risk factors for VTE, HRT should be avoided. If HRT is to be used, a clear discussion of the potential excess risk should occur with the woman and transdermal therapy may be best. As this remains a controversial and rapidly developing area, advice should be sought from clinicians with special expertise in thrombophilia. [Evidence Level 4]

How Should HRT be Managed in Those with a Previous VTE?

C - A personal history of thrombosis is a contraindication to oral HRT.

D - If it is considered that quality of life is so severely affected that the benefits of HRT outweigh the risks, a transdermal preparation should be used.

If it is considered that HRT is desirable for a particular woman, the risk of recurrence should be discussed carefully with her and she must be advised to report promptly if any symptoms compatible with VTE arise. Where HRT is to be used in those with prior VTE, prophylactic anticoagulant therapy may be considered while the woman is taking HRT. However, if anticoagulant thromboprophylaxis has to be used, the risk of haemorrhage must be considered in the risk–benefit analysis. On standard anticoagulant thromboprophylaxis, major haemorrhage occurs at a rate of around 1% per year of treatment and 25% of these bleeds are fatal.

As discussed above, transdermal therapy may be best in such a situation. Specialist advice from a clinician with expertise in thrombosis and thrombophilia should be sought.

Testing for thrombophilia in selected women (e.g., those with previous severe unprovoked or recurrent VTE) may be helpful in assessing the overall thrombotic risk in women with a personal history of VTE, but the result will not alter the advice that oral HRT should be avoided. In general, testing for thrombophilia in unselected women who have experienced a first episode of VTE is not routinely recommended, as there is insufficient evidence that testing reduces the risk of recurrence or that the results should influence the duration of anticoagulant therapy. Testing when a severe defect (such as deficiency of antithrombin, protein C or protein S) is suspected may be helpful in assessing the overall thrombotic risk. If thrombophilia testing is suggested, the limitations of testing should be discussed.

How Should HRT Be Managed in Those Who Develop VTE While Receiving HRT?

C - It is recommended that, when a woman who is on HRT develops a VTE, HRT should be discontinued.

What Other Risk Factors Should Be Considered When Assessing the Risk of VTE Associated with HRT?

C - Before commencing HRT, any personal or family history of VTE should be assessed.

C - A history of VTE in a first-degree relative (i.e., parent, sibling or offspring) is a relative contraindication to HRT.

D - Where there is a family history in a first-degree relative, alternatives to oral HRT should be suggested. If HRT is considered desirable, transdermal preparations are associated with a significantly lower risk of venous thrombosis.

As VTE is usually dependent on multiple risk factors coming together, it is important to be aware of the presence of pre-existing thrombotic risk factors. The prescriber should specifically ask whether there is a previous personal history of VTE or a history of VTE in a first-degree relative. The presence of multiple pre-existing risk factors for VTE may suggest that HRT, itself a risk factor, might be best avoided. In particular, women with a previous VTE are at high risk of recurrence. However, it is important to review the overall situation for each individual. Given the polygenic nature of VTE, even where a familial thrombophilia has been identified, the risk of VTE may also be increased in those members of the family who do not carry that thrombophilia. Consequently, a negative thrombophilia result does not necessarily exclude an increased risk. Therefore, thrombophilia testing may not be informative in predicting risk without consideration of individual risk factors and the nature of the family history. Where a heritable thrombophilia has been detected in an affected family member, testing for heritable thrombophilia will not provide a definitive estimate of risk in most cases and is not routinely recommended. However, where a high-risk heritable thrombophilia has been identified in a symptomatic family member (e.g., deficiency of antithrombin, protein C or protein S), testing for thrombophilia may assist in the counselling of overall thrombotic risk. [Evidence Level 2+]

D - HRT should be avoided in women with multiple pre-existing risk factors for VTE.

Multiple defects or combinations of acquired and/or inherited risk factors are likely to be important in VTE risk. Such additional risk factors include patient factors, as detailed below. Consequently, the increase in relative risk associated with HRT has to be viewed in the context of that associated with other risk factors and the potential for interaction between risk factors should not be underestimated.

Additional risk factors for venous thromboembolism

- Increasing age
- Obesity (body mass index >30)
- Previous VTE
- Post-thrombotic syndrome
- Varicose veins with phlebitis
- First-degree family history of VTE
- Immobility for more than 3 days
- Surgical procedures (anaesthesia and surgical time >60 minutes)
- Other disorders, e.g., malignancy, myeloproliferative disorders, cardiac disease, paralysis of lower limbs, systemic infection, inflammatory bowel disease, nephritic syndrome, sickle cell disease

Definitions:

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B - A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Venous thromboembolism associated with hormone replacement therapy

Guideline Category

Counseling

Management

Prevention

Risk Assessment

Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Preventive Medicine

Intended Users

Physician Assistants

Physicians

Guideline Objective(s)

To enable physicians to assess thrombotic risk in patients undergoing or starting hormone replacement therapy

Target Population

Women undergoing or considering hormone replacement therapy

Interventions and Practices Considered

Assessment/Counseling

1. Personal and family history of venous thromboembolism (VTE) or risk factors for VTE
2. Counselling of women starting or continuing hormone replacement therapy (HRT) concerning risk of VTE, HRT delivery systems, and alternative therapy
3. Thrombophilia screening (for women with a personal or family history of VTE*)

Management

1. Avoidance of oral HRT in women with personal or family history of VTE or multiple risk factors for VTE
2. Use of transdermal HRT in women with personal or family history of VTE
3. Discontinuation of HRT in women who develop a VTE
4. Consultation with a clinician with expertise in thrombosis and thrombophilia

*Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT was considered but not recommended.

Major Outcomes Considered

Risk for and incidence of venous thromboembolism (VTE) associated with hormone replacement therapy (HRT)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This guideline was developed using the standard methodology for developing Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines (see the "Availability of Companion Documents" field). Original articles for the evidence base for this guideline were obtained following a computer search for 'hormone replacement' as a keyword and also in combination with 'venous thrombosis' or 'deep venous thrombosis' (DVT) or 'pulmonary embolism' or 'thrombophilia' applied to Medline (1966 to week 1, 2010), EMBASE (1980 to week 1, 2010), Evidence-based Medicine Reviews, the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness to the last quarter of 2009. This was complemented by hand searching for individual references identified from these original articles.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Reviewing and Grading of Evidence

Once the evidence has been collated for each clinical question it needs to be appraised and reviewed (refer to section 3 in "Development of RCOG Green-top guidelines: producing a clinical practice guideline" for information on the formulation of the clinical questions; see the "Availability of Companion Documents" field). For each question, the study type with least chance of bias should be used. If available, randomised controlled trials (RCTs) of suitable size and quality should be used in preference to observational data. This may vary depending on the outcome being examined.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency, and applicability of the evidence base. The methods used to appraise individual study types are available from the SIGN Web site (www.sign.ac.uk/methodology/checklists.html). An objective appraisal of study quality is essential, but paired reviewing by guideline leads may be impractical because of resource constraints.

Once evidence has been collated and appraised, it can be graded. A judgement on the quality of the evidence will be necessary using the grading system (see the "Rating Scheme for the Strength of the Evidence" field). Where evidence is felt to warrant 'down-grading', for whatever reason, the rationale must be stated. Evidence judged to be of poor quality can be excluded. Any study with a high chance of bias (either 1– or 2–) will be excluded from the guideline and recommendations will not be based on this evidence. This prevents recommendations being based on poor-quality RCTs when higher-quality observational evidence is available.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development

The development of guidelines involves more than the collation and reviewing of evidence. Even with high-quality data from systematic reviews of randomised controlled trials, a value judgement is needed when comparing one therapy with another. This will therefore introduce the need for consensus.

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines are drafted by nominated developers, in contrast to other guideline groups such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who use larger guideline development groups. Equally, in contrast to other guideline groups, the topics chosen for development as Green-top guidelines are concise enough to allow development by a smaller group of individuals.

In agreeing the precise wording of evidence-based guideline recommendations and in developing consensus-based 'good practice points', the Guidelines Committee (GC) will employ an informal consensus approach through group discussion. In line with current methodologies, the entire development process will follow strict guidance and be both transparent and robust. The RCOG acknowledges that formal consensus methods have been described, but these require further evaluation in the context of clinical guideline development. It is envisaged that this will not detract from the rigor of the process but prevent undue delays in development.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B - A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Cost Analysis

The cost-effectiveness of screening women for thrombophilia has been examined in a number of at-risk clinical circumstances and screening selected women before prescribing oral hormone replacement therapy (HRT) may be the most cost-effective method. However, on the available evidence, universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of HRT is inappropriate and should be discouraged.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Following discussion in the Guidelines Committee (GC), each Green-top guideline is formally peer reviewed. At the same time, the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) Web site for further peer discussion before final publication.

All comments will be collated by the RCOG and tabulated for consideration by the guideline leads. Each comment will require discussion. Where comments are rejected then justification will need to be made. Following this review, the document will be updated and the GC will then review the revised draft and the table of comments.

Once the GC signs-off on the guideline, it is submitted to the Standards Board for approval before final publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of women with hormone replacement therapy, and prevention of thromboembolism in patients at risk

Potential Harms

Side effects associated with hormone replacement therapy and anticoagulant thromboprophylaxis

Contraindications

Contraindications

- A personal history of thrombosis is a contraindication to oral hormone replacement therapy (HRT).
- A history of venous thromboembolism (VTE) in a first-degree relative (i.e., parent, sibling or offspring) is a relative contraindication to hormone replacement therapy.

Qualifying Statements

Qualifying Statements

- These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research might be indicated.

- The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health services. This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Venous thromboembolism and hormone replacement therapy. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 May. 16 p. (Green-top guideline; no. 19). [87 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2004 Jan (revised 2011 May)

Guideline Developer(s)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

Source(s) of Funding

Royal College of Obstetricians and Gynaecologists

Guideline Committee

Guidelines Committee

Composition of Group That Authored the Guideline

Authors: Professor IA Greer FRCOG, Liverpool, Professor ID Walker, Department of Haematology, University of Glasgow; Dr P Clark, Consultant Haematologist and Honorary Reader, Scottish National Blood Transfusion Service, Dundee

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Committee Lead Reviewers: Mrs CE Overton FRCOG, Bristol; Mr P Owen, MRCOG, Glasgow, Scotland

Financial Disclosures/Conflicts of Interest

Conflicts of interest: none declared

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Royal College of Obstetricians and Gynaecologists (RCOG). Hormone replacement therapy and venous thromboembolism. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2004 Jan. 9 p. (Guideline; no. 19).

Guideline Availability

Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .

Availability of Companion Documents

The following are available:

- Development of RCOG Green-top guidelines: policies and processes. Clinical Governance Advice No 1a. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 6 p. Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .
- Development of RCOG Green-top guidelines: producing a scope. Clinical Governance Advice No 1b. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 4 p. Electronic copies: Available from the RCOG Web site

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- Development of RCOG Green-top guidelines: producing a clinical practice guideline. Clinical Governance Advice No 1c. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 13 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: consensus methods for adaptation of Green-top guidelines. Clinical Governance Advice No 1d. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Feb. 9 p. Electronic copies: Available from the RCOG Web site .

In addition, suggested audit topics can be found in section 12 of the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on October 14, 2005. This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This summary was updated by ECRI Institute on December 26, 2008 following the FDA advisory on Innohep (tinzaparin). This NGC summary was updated by ECRI Institute on January 26, 2012.

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